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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,036	KAUMAYA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2005 and 22 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,21,22,25-29 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *21,22,25-29, 31-33, 37, and 38* is/are withdrawn from consideration.

5)☒ Claim(s) *35* is/are allowed.

6)☒ Claim(s) *1,4-8,34 and 36* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050317*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.00-

DETAILED ACTION

1. The amendment filed March 15, 2005 is acknowledged and has been entered.

2. The supplemental amendment filed June 22, 2005 is acknowledged and has been entered. Claims 9, 11-20, and 30 have been canceled. Claims 1, 3, 4, 6-8, 21, 22, 25-29, and 31-33 have been amended. Claims 34-38 have been added.

3. Claims 1, 3-8, 21, 22, 25-29, and 31-38 are pending in the application. Claims 21, 22, 25-29, 31-33, 37, and 38 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim.

4. Claims 1, 3-8, and 34-36 are currently under prosecution.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Information Disclosure Statement

7. The information disclosure filed March 15, 2005 has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

8. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed October 15, 2004.

Response to Amendment

9. Applicant is reminded that in response to a Notice of Non-Compliant Amendment, such as that mailed June 17, 2005, Applicant's reply should consist of only the corrected section of the non-compliant amendment (in its entirety), e.g., the entire "Amendments to the Claims" section of the amendment. See MPEP § 714.03. In this instance, as noted on the Notice of Non-Compliant Amendment, the amendment filed March 15, 2005 was not compliant because claims 7 and 8 were not provided in the listing of claims with the proper status identifier (i.e., Currently Amended); accordingly only the "Amendment to the Claims" section of the amendment should have been provided in response to the Notice.

Election/Restrictions

10. Beginning at page 17 of the amendment filed March 15, 2005 Applicant has affirmed the provisional election made with traverse to prosecute the invention of Group I, claims 1, 3-8, and 31 and the species of invention, wherein said composition comprises the HER2 B cell epitopes of SEQ ID NO: 6 and SEQ ID NO: 42.

Applicant has traversed the restriction and election requirement, arguing that the requirement is not proper because to be proper searching more than one independent or distinct invention must be a serious burden on the examiner. More particularly, Applicant has argued that it would not be unduly burdensome to search claims directed to the inventions of Groups I and III together, since "the various pharmceutically [sic] acceptable vehicles have been removed from process claims 27-29" (page 18, paragraph 2). In reply, claims 27-29 are directed to a process for treating cancer in a subject comprising administering to the subject a pharmaceutical composition comprising a pharmaceutically acceptable vehicle and a chimeric peptide. In contrast, the elected invention is a product, namely a chimeric peptide. The Office action mailed October 15, 2004 established reasons that the inventions of Groups I and III are patentably distinct and given that the inventions of Group I are products, whereas the inventions of Group III are processes for using such products, the search required to consider claims directed to the inventions of Group I is not the same, nor is it

coextensive with the search required to consider claims directed to the inventions of Group III. Therefore, consideration of claims directed to the inventions of Group III would require the performance of a search that is not necessary to consider claims directed to the elected inventions. A need to perform such an additional search would constitute a serious burden.

At page 18, paragraph 3, of the amendment filed March 15, 2005 Applicant has requested rejoinder, under the provisions of MPEP § 821.04, of the withdrawn process claims 21, 22, 25-29, 32, and 33 (Group III). In response, at this time the request is denied. As explained at page 14 of the Office action mailed October 15, 2004, process claims that depend from or otherwise include all the limitations of a product claim subsequently found to be allowable will be rejoined in accordance with those provisions. Claim 35, drawn to a product, is allowed herein; however, none of the process claims that are withdrawn from further consideration depend from or otherwise include all the limitations of claim 35.

At page 18, paragraph 4, Applicant has argued that claim 31 should be examined together with claims directed to the elected species of invention, because a search for the elected species of invention should also uncover a multivalent peptide or mixture of chimeric peptides in which the sequences of three HER2 B cell epitopes are SEQ ID NOs: 6, 42, and 9, and therefore it would not be a serious burden to also consider claim 31. In reply, consideration of claim 31, directed to a species of the invention of claim 6, wherein the sequence of one of said HER2 B cell epitopes is SEQ ID NO: 9, would require a search of relevant sequence databases using SEQ ID NO: 9 as a query. Thus, consideration of claim 31 would require a search that is not required for consideration of claims directed to the elected species of invention. Moreover, the search necessary to consider the subject matter of claim 31 is not the same, nor is it coextensive with the search necessary to consider the elected species of invention. Having to perform an additional search to consider claim 31 in addition to claims directed to the elected species of invention would constitute a serious burden.

11. Applicant's amendment has obviated or rendered moot the rejection of claims 1 and 3-5 under 35 U.S.C. § 112, first paragraph for the reasons set forth in sections 25 and 26 of the Office action mailed October 15, 2004. Accordingly, Applicant's amendment has necessitated consideration of a species of invention, which was previously withdrawn from further consideration until such a time that the generic claims were deemed allowable over the requirements set forth under 35 U.S.C. § 112, first paragraph. Therefore, in this Office action, claims 1 and 3-5 have been considered to the additional extent to which those claims read on the first named species of invention, wherein the sequence of the HER2 B cell epitope is SEQ ID NO: 1.

12. Newly submitted claims 37 and 38 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons:

Claim 37 is drawn to the method of claim 36, which is the subject matter of a non-elected invention; moreover, although claim 36 is drawn to a composition, not a method, it is presumed that claim 37 is drawn to an invention that is patentably distinct from each of the other claimed inventions, including the elected invention, and that consideration of the claimed subject matter would be unduly burdensome because it would require a search that is not the same, nor coextensive with the search required to consider claims drawn to any of the other inventions, including the elected invention.

Claim 38 is drawn to the method of claim 32. Claim 32 has been withdrawn from further consideration for reasons already of record and because claim 38 depends from claim 32, claim 38 is directed to the subject matter of a non-elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 37 and 38 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

13. The rejection of claims 6-8, 34, and 36 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At page 19 of the amendment filed March 15, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Applicant has argued that claim 6 has been amended to recite that the template comprises two strands of alternating leucine and lysine residues connected by a linker consisting of one to fifteen amino acids. However, claim 6, as well as newly added claim 36, is directed to a genus of "templates", wherein each of the B cell epitopes and T helper cell epitopes are attached to a member of this genus. This genus of templates to which the claim is directed includes polypeptides but are not necessarily limited to polypeptides but may instead comprise inorganic or non-peptide, organic materials comprised of two strands of alternating leucine and lysine residues; moreover, the genus includes polypeptides that are "core β sheets", but are not necessarily limited to such polypeptides, since a template comprising two strands of alternating leucine and lysine residues connected by a peptide linker of varying amino acid composition and

length or affixed to an organic or inorganic material does not necessarily form a "core β sheet".

As explained in the Office action mailed October 15, 2004, the specification teaches a single member of the genus of "templates", which is a polypeptide, which is described essentially as a "core β sheet", that presumably forms the secondary structure of a β-sheet and comprises a primary structure of two strands of alternating leucine and lysine residues connected by a linker; see, e.g., page 4, lines 27-29. Although this embodiment of the "template" is preferred, the claims are reasonably drawn to a chimeric peptide comprising a template that is any material comprising two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids, which is suitable for attaching the peptides comprising the B cell and T helper cell epitopes. The claims are not limited to a template that is a polypeptide, or consists of a polymer of amino acids.

The specification does not describe other "templates", including other "core β sheets", or other material suitable for making such "templates" and "core β sheets". For example, the specification does not include a description of any member of the genus of templates composed of an inorganic material to which two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids are attached, which is suitable for attaching the peptides comprising the B cell and T cell epitopes; nor does the specification describe any one of the templates composed of the wide variety of non-peptide organic materials (e.g., sugars, lectins) to which two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids are attached, which are also suitable.

Accordingly, given the instant written description of the claimed invention, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of templates to which the epitopes are attached. Therefore, the written description would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

In summary, the specification provides an adequate written description of a template that is a polypeptide that forms a β sheet, which comprises two strands of alternating leucine and lysine residues connected by a linker, which can be used as a scaffold for the attachment of multiple peptides comprising B and T cell epitopes, but does not provide an adequate written description of at least a substantial number of the members of the genus of "templates" comprising two strands of alternating leucine and lysine residues adjoined by a linker of 1 to 15 amino acids. Therefore, the instant disclosure of the claimed invention is insufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph.

14. The rejection of claims 6-8, 34, and 36 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a composition for stimulating an immune response to HER-2 protein, wherein said composition comprises a multivalent peptide comprising: (i) the HER-2 B cell epitope of SEQ ID NO: 6, (ii) the HER-2 B cell epitope of SEQ ID NO: 42, (iii) a T helper cell epitope selected from the group consisting of the T helper cell epitopes taught by the prior art, including those of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 or a functional equivalent thereof comprising the amino acid sequence LSLIKGVIVHRLEGV, as taught by the prior art, SEQ ID NO: 18, and SEQ ID NO: 19, and (iv) a polypeptide to which each of said epitopes are connected, which polypeptide comprises two strands of alternating leucine and lysine residues connected by the linker of one to fifteen amino acids *and forms a β sheet*, **does not reasonably provide enablement for making** the claimed compositions comprising multivalent peptides comprising *any type of template* adjoining the HER-2 B cell epitope and said T helper epitope and comprising two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids, is maintained.

At page 19 of the amendment filed March 15, 2005 Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Applicant has argued that, as amended, the claims are directed to subject matter that is fully enabled by the supporting disclosure. Although the specification teaches a template that is a polypeptide that forms a "core β sheet" and consists of two strands of alternating leucine and lysine residues connected by an amino acid linker or a peptide, given the broadest reasonable interpretation, claims 6 and 36 are directed to a "template" that is any material (organic or inorganic) comprising two strands of

alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids to which the B cell and T cell epitopes can be attached.

The specification only provides sufficient guidance, direction, and exemplification to make a template suitable for adjoining the B cell and T cell epitopes, which is comprised of a polypeptide that forms a β sheet and comprises two strands of alternating leucine and lysine residues adjoined by a linker that is a peptide of from about 2 to about 15 amino acids in length and comprises SEQ ID NO: 20. The specification, for example, does not teach the skilled artisan to make a template that is composed of an inorganic material comprising two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids, which is suitable for attaching the peptides comprising the B cell and T cell epitopes; nor does the specification provide the teachings necessary to enable the skilled artisan to make the wide variety of non-peptide organic materials (e.g., sugars, lectins) comprising two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids, which are suitable.

As explained in the Office action mailed October 15, 2004, Kaumaya et al. teaches that to be suitable and effective, a carrier or template as to which the claims are drawn must allow the incorporation of stabilized conformational determinants, such as the epitopes described in the instant specification, such that those determinants mimic the shape of the sequence in the native protein (page 157). Furthermore, Kaumaya et al. teaches if this criterion is not met, simply increasing the number of epitopes will not yield antibodies of high affinity or specificity (page 157).

The skilled artisan cannot predict which materials are, or whether any given material is, suitable for use as such a template; and therefore, the specification provides an insufficient amount of guidance, direction, and exemplification to enable the skilled artisan to physically attach the epitopes to at least a substantial number of the structurally variable members of the genus of suitable "templates". Thus, because the skilled artisan would be left to discover other suitable materials, which are usable as "templates" by determining the chemical means by which the B cell and T cell epitopes could be attached to candidate materials and whether the B cell and T cell epitopes

attached thereto elicit an effective humoral immune response against HER-2, the skilled artisan could not make and then use the claimed invention without first performing undue and/or unreasonable experimentation.

Furthermore, although the specification teaches a template comprising two strands of alternating leucine and lysine residues adjoined by the peptide linker of SEQ ID NO: 20, which forms a β sheet and is suitable for making the claimed invention, the skilled artisan cannot reliably predict whether a "template" comprised two strands of alternating leucine and lysine residues forms a β sheet, which is suitable for use in making a multivalent chimeric peptide capable of such a function. The prior art, e.g., Kaumaya et al. (cited *supra*), teaches a polypeptide consisting of two polypeptide strands of alternating leucine and lysine residues connected by a peptide linker consisting of an amino acid sequence identical to SEQ ID NO: 20 forms a β sheet structure is suitable for use as a template or scaffold for the attachment of a plurality of B and T cell epitopes. Kaumaya et al. teaches this template allows the B cell and T cell epitopes to be affixed in any combination or orientation and the resultant multivalent chimeric peptides are effective in stimulating a humoral immune response against a native protein (pages 157-159).

However, neither the prior art, nor the specification, teach other "templates", including polypeptides consisting of two strands of alternating leucine and lysine residues adjoined by a linker of 1 to 15 amino acids, which form β sheets, which have had demonstrable suitability in their use as a template or scaffold for the attachment of a plurality of B and T cell epitopes in the manufacture of a multivalent chimeric peptide capable of stimulating an effective humoral immune response against a native protein. As explained in the preceding Office action, although many different methods have been proposed for predicting the secondary structure of a polypeptide, Kyngas et al. (of record), for example, teaches that trying to predict the three-dimensional structure of a protein from its amino acid sequence remains one of the most challenging problems in bioscience; see entire document (e.g., the abstract). In particular, Kyngas et al. teaches that the well-known Chou-Fasman parameters used in predicting protein secondary

structure is are unreliable; see, e.g., the abstract. Furthermore, with emphasis on the ability to reliably predict the propensity of a polypeptide to form a β sheet, Pal et al. (of record) and Street et al. (of record), for examples, teach although progress has been made in understanding the many factors that determine the stability of α helices, our understanding of the factors that determine β sheet stability is much less advanced. Street et al. teaches no concise theoretical description that fully explained β-sheet propensities of the naturally occurring amino acids has yet emerged from our endeavours to understand these factors; see, e.g., page 9074, column 2. The amount of guidance, direction, and exemplification fails to provide the skilled artisan with solutions to the current problems and limitations affecting the reliability of predicting whether polypeptides, which might be suitable for use as templates to which the B cell and T cell epitopes can be attached, have a propensity to form β sheets.

Were the template further limited to *a polypeptide that forms a β sheet* comprising two strands of alternating leucine and lysine residues connected by a linker, for these same reasons, the skilled artisan cannot reliably predict which polypeptides will adopt the conformation of a β sheet, since one skilled in the art cannot predict which linkers (i.e., which amino acids or which peptides) can be used to connect the two strands of alternating leucine and lysine residues, such that the resultant polypeptide forms a β sheet. Again, as explained previously, the prior art (e.g., Kaumaya et al.) teaches that a polypeptide "template" comprising two strands of alternating leucine and lysine residue adjoined by a linker consisting of an amino acid sequence that is identical to SEQ ID NO: 20, which adopts the secondary conformation of a β sheet. However, other linkers, which are also suitable have not been described by the prior art, nor has the specification provided guidance and direction to enable the skilled artisan to determine which other linkers can be used, so that the claimed invention can be made, and thus used, without having to first perform an undue amount of additional experimentation to identify and characterize such linkers.

With particular regard to claim 34, which recites that the linker connecting the two strands of alternating leucine and lysine residues of which the template is comprised

consists of the amino acid sequence identified as SEQ ID NO: 20 (i.e., Gly-Pro-Ser-Leu). At page 5, lines 1 and 2, the specification teaches that the most preferred linker used in constructing the template to which the claim is directed comprises this particular sequence; however, the specification does not exemplify its use in constructing a template that adopts the essential structure of a core β sheet. While Kaumaya et al. (of record; cited *supra*) does not expressly teach the composition of linkers used in constructing suitable "templates", it is noted that elsewhere the prior art teaches the linker consists of the 6 amino acid sequence of Gly-Leu-Pro-Ser-Gly-Gly. See, for example, Lairmore et al. (*J. Virol.* 1995 Oct; **69** (10): 6077-6089), which teaches this linker is used to adjoin two strands of alternating leucine and lysine residues to form a template having the essential β sheet conformation; see entire document (e.g., page 6078, Figure 1; and page 6087, paragraph bridging columns 1 and 2). The prior art, nor the specification, however, teach that two strands of alternating leucine and lysine residues that are adjoined by any other linker, such as a linker consisting of the amino acid sequence of SEQ ID NO: 20 will form a β sheet, or be suitable for use in making the claimed invention, which is to be used in stimulating a specific humoral immune response against HER-2. Undue and unreasonable experimentation would be necessary before the claimed invention could be made and used in accordance with the guidance set forth in the instant application, because it cannot be predicted whether the template comprising such a linker adjoining the two strands of alternating amino acid residues will form the essential β sheet and be suitable for use in constructing the claimed invention.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

New Ground of Claim Objection

15. Claim 3 is objected to because the claim recites, "wherein the sequence of the HER 2-B is [...]". The claim should read, "wherein the sequence of the HER-2 B cell epitope is [...]". Appropriate correction is required.

After such appropriate correction, it is duly noted that claim 3 would be objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

16. Claims 1, 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbine (Doctoral Dissertation: "BIOLOGICAL EFFECTS OF ANTI-PEPTIDE ANTIBODIES AGAINST THE HER-2/NEU RECEPTOR TYROSINE KINASE: IMPLICATIONS FOR THERAPY OF HUMAN BREAST CANCER", The Ohio State University, 1997) (of record) in view of Partidos et al. (*Mol. Immunol.* 1997 Nov-Dec; 34 (16-17): 1105-1111), WO 98/17797 A1, and Harwerth et al. (*British Journal of Cancer.* 1993 Dec; **68** (6): 1140-1145) (of record).

The claimed invention:

Claims 1, 4, and 5 are drawn to a composition that is a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 1, which is adjoined by a linker of SEQ ID NO: 20 to a T helper epitope comprising SEQ ID NO: 17.

The primary reference teaches or suggests:

Woodbine teaches chimeric peptides that comprise: (a) a HER-2 B cell epitope comprising SEQ ID NO: 42, (b) a T helper cell epitope derived amino acids 288-302 of the measles virus F protein (MVF), and (c) a linker consisting of an amino acid sequence identical to SEQ ID NO: 20 (gly-pro-ser-leu), which adjoins the HER-2 B cell epitope and the T helper cell epitope to form a colinear construct; see entire document (e.g., page 63 and page 74, Figure 8). More particularly, Woodbine teaches four

different chimeric peptides: "DW1MVF (Her-2 376-395)", which comprises a HER-2 B cell epitope comprising amino acids 376-395 of HER-2; "MVFDW4 (628-647)", which comprises a HER-2 B cell epitope comprising amino acids 628-647 of HER-2; "DW5MVF (115-136)", which comprises a HER-2 B cell epitope comprising amino acids 115-136 of HER-2; and "DW6MVF (410-429)", which comprises a HER-2 B cell epitope comprising amino acids 410-429 of HER-2 (page 63). Each of the chimeric peptides comprises a linker having an amino acid sequence that is identical to SEQ ID NO: 20, as disclosed by the instant application, which adjoins the HER-2 B cell epitope and a T helper cell epitope; see, e.g., page 74, Figure 8. Woodbine teaches the chimeric peptides are highly immunogenic, as evidenced by high antibody titers as early as the third week post immunization (page 83). Woodbine teaches the antibodies produced by immunizing the animals with the different chimeric peptides is immunoreactive with the extracellular domain of HER-2 by showing that the antibodies bind SKBR3 cells; see, e.g., pages 84 and 85. Woodbine teaches these antibodies bind HER-2-expressing breast cancer cells and selectively inhibit tumor cell proliferation *in vitro*; see, e.g., page iii. Moreover, Woodbine teaches the anti-peptide antibodies produced by the immunizing animals with the chimeric peptides retarded tumor growth in a nude mouse model. Accordingly, Woodbine suggests the antibodies raised to a peptide vaccine in humans may offer an effective, selective, and less toxic system of HER-2 positive tumor management than currently available methods, particularly since such synthetic vaccines would also avoid the dangers involved in using attenuated strains of viruses or infectious biological material as carriers and provide a cost-effective method of treatment; see, e.g., page iii.

Notably, the chimeric peptide "MVFDW4 (628-647)" comprises a HER-2 B cell epitope that is identical to the HER-2 B cell epitope set forth as SEQ ID NO: 42 in the instant application; see page 77, Figure 15. Woodbine teaches the amino acid sequence of the native epitope was altered by substituting glycine for the cysteine at position 3 of the sequence (pages 77 and 78).

Additionally, it is noted that the chimeric peptides of Woodbine comprise a T helper epitope comprising an amino acid sequence that is different from the amino acid

sequence set forth as SEQ ID NO: 17; see, e.g., page 74, Figure 8. The third amino-terminal amino acid of SEQ ID NO: 17 is glutamic acid; whereas the amino acid at the corresponding position of the T helper epitope of Woodbine is a leucine. However, because Woodbine teaches a chimeric peptide comprising the disclosed Th cell epitope is derived from amino acids 288-302 of MVF and is functional, the Th epitope disclosed by Woodbine is deemed the same as or at least a functional equivalent of the Th epitope of SEQ ID NO: 17, which the specification also describes as amino acids 288-302 of MVF (e.g., page 23, lines 23 and 24).

The primary reference does not explicitly teach or suggest:

Woodbine does not teach a chimeric peptide according to claim 1, which comprises a HER-2 B cell epitope, wherein the sequence of said HER-2 B cell epitope is SEQ ID NO: 1 (i.e., a chimeric peptide comprising the sequence of SEQ ID NO: 1, a T helper epitope and a linker joining both).

Furthermore, as explained above, Woodbine does not teach a T helper epitope that comprises the amino acid sequence set forth as SEQ ID NO: 17, but does teach a T helper epitope that comprises amino acids 288-302 of MVF, which is nearly identical to the amino acid sequence identified by SEQ ID NO: 17.

The secondary references teach or suggest:

Partidos et al. teaches the amino acid sequence of amino acids 288-302 of MVF, which is a T helper epitope, is the sequence identified in this application as SEQ ID NO: 17; see entire document (e.g., page 1106, Table 1).

WO 98/17797 A1 (Fendly et al.) teaches a peptide comprising the HER-2 B cell epitope having the amino acid sequence identified in the instant application as SEQ ID NO: 1; see entire document (e.g., SEQ ID NO: 2). Moreover, Fendly et al. teaches this peptide, which has the amino acid sequence identified as SEQ ID NO: 2, comprises the epitope to which monoclonal antibodies 7C2 and 7F3 bind. Fendly et al. teaches the amino acid sequence identified as SEQ ID NO: 2 corresponds to amino acids 22-53 of the amino acid sequence of HER-2; see, e.g., Figure 13. Fendly et al. teaches the antibody that binds to this epitope of HER-2 induces breast tumor cells expressing HER-2 to undergo apoptosis; see, e.g., Figure 5. In addition, it is aptly noted that

Fendly et al. teaches the use of peptides, such as the peptide of SEQ ID NO: 2 to elicit an immune response in a subject and thereby stimulate the production of antibodies that bind to such peptides; see, e.g., page 17. Fendly et al. teaches it is useful to conjugate the peptides or relevant antigens to a protein that is immunogenic in the species to be immunized (page 17).

Harwerth et al. teaches a combination of two monoclonal antibodies, which antibodies react with two distinct epitopes of the extracellular domain of HER-2, more effectively retarded the growth of HER-2-postive tumors in nude mouse models, as compared to either of the antibodies alone; see entire document (e.g., the abstract).

The obviousness of the claimed invention:

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have produced a composition comprising a combination of two functionally equivalent chimeric peptides, wherein one of said chimeric peptides comprises the B cell epitope of SEQ ID NO: 1, which is disclosed by Fendly et al. as SEQ ID NO: 2, a T helper epitope comprising amino acids 288-302 of MVF, or SEQ ID NO: 17, as disclosed by Partidos et al., and a linker adjoining both, as disclosed by Woodbine, and wherein the other of said chimeric peptides comprises the B cell epitope of SEQ ID NO: 42 adjoined by a linker to the T helper epitope comprising the amino acids 288-302 of MVF, as disclosed by Woodbine, because Partidos et al. teaches the amino acid sequence of the T helper epitope comprising amino acids 288-302 of MVF is SEQ ID NO: 17, Fendly et al. teaches antibodies that bind this epitope of HER-2 induce breast cancer cells expressing HER-2 to undergo apoptosis and Woodbine teaches such chimeric peptides elicit antibodies reactive against different epitopes of the extracellular domain of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, whereas Harwerth et al. teaches a combination of antibodies reactive against different epitopes of the extracellular domain of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, can be used more effectively than any of the antibodies alone. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to produce a composition that can be used to more effectively retard the growth of HER-2-positive tumors.

17. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbine DB (Doctoral Dissertation: "BIOLOGICAL EFFECTS OF ANTI-PEPTIDE ANTIBODIES AGAINST THE HER-2/NEU RECEPTOR TYROSINE KINASE: IMPLICATIONS FOR THERAPY OF HUMAN BREAST CANCER", The Ohio State University, 1997) (of record) in view of WO 98/17797 A1, Kaumaya et al. (Peptides: Design, Synthesis, and Biological Activity, Basava et al., Eds., Birkhauser: Boston, 1994) (of record), and Lairmore et al. (*J. Virol.* 1995 Oct; **69** (10): 6077-6089).

The claimed invention:

Claim 1 is drawn to a composition that is a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 1, which is adjoined by a linker of 1 to 15 amino acids to a T helper epitope comprising SEQ ID NO: 17. Accordingly, claim 1 reads on a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 1 and a T helper epitope comprising SEQ ID NO: 17, which are affixed to a common polypeptide ("template") comprising two adjoined strands of alternating leucine and lysine residues and which are thereby joined by "a linker of 1 to 15 amino acids" to one another.

Claim 6 is drawn to a "multivalent chimeric peptide" comprising two or more different HER-2 B cell epitopes a T helper epitope, and a polypeptide comprising two strands of alternating leucine and lysine residues adjoined by a linker comprising SEQ ID NO: 20, each of which are joined to a polypeptide linker ("template") consisting of two strands of alternating leucine and lysine residues connected by a peptide linker of 1 to 15 amino acids, which form a β sheet, wherein one of said chimeric peptides comprises a HER-2 B cell epitope comprising SEQ ID NO: 1 and another of said chimeric peptides comprises a HER-2 B cell epitope comprises SEQ ID NO: 42, wherein said T helper epitope is selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

The primary reference teaches or suggests:

Woodbine teaches that which is set forth in the above rejection of claims 1, 4, and 5 under 35 USC § 103(a).

The primary reference does not explicitly teach or suggest:

Woodbine does not explicitly teach a composition that is a chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 1 and a T helper epitope comprising SEQ ID NO: 17, which are affixed to a common polypeptide comprising two adjoined strands of alternating leucine and lysine residues and thereby joined by "a linker of 1 to 15 amino acids" to one another, as encompassed by claim 1.

Furthermore, Woodbine does not explicitly teach "multivalent chimeric peptide" comprising more than one HER-2 B cell epitopes, each of which is attached or linked to a common polypeptide, or "template" comprising two strands of alternating leucine and lysine residues connected by a linker of 1 to 15 amino acids, wherein one of said HER-2 B cell epitopes comprises SEQ ID NO: 1 and another comprises SEQ ID NO: 42, wherein said T helper epitope is selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

The secondary references teach or suggest:

WO 98/17797 A1 (Fendly et al.) teaches that which is set forth in the above rejection of claims 1, 4, and 5 under 35 USC § 103(a).

Kaumaya et al. teaches *multivalent B cell chimeric peptide vaccines*, which comprise a plurality of the same or different B cell epitopes and a plurality of T helper cell epitopes covalently attached to either strand of a "β sheet template", which is a polypeptide comprising two strands of alternating leucine and lysine residues connected by a linker; see entire document, particularly pages 157-159 and Figure 9-7. Kaumaya et al. teaches the advantage to using the disclosed "β sheet template" to produce a multivalent chimeric peptide is that it allows multiple B- and T-cell epitopes to be linked in any combination and orientation, such that the epitopes have a stabilized conformation that mimics the shape of the sequence in the native protein (page 157). Kaumaya teaches T helper cell epitopes comprising SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19 are "promiscuous", since the epitopes function to stimulate immune responses in animals of multiple different haplotypes and are thus not haplotype-restricted, or

haplotype-specific (pages 153 and 154). Kaumaya teaches the multivalent chimeric peptides are extremely immunogenic, inducing high-titered antibodies specific for the native protein (page 158). Kaumaya et al. teaches the multivalent chimeric peptides produced enhanced immune responses in animals, as compared to those produced by colinear chimeric peptide comprising the same B cell epitope adjoined to same T helper cell epitope by a linker (page 157). Furthermore, Kaumaya et al. teaches that by grafting dual copies of the B cell epitopes onto the "template", they were able to raise antibodies in the strains of animals, which did not respond to the colinear chimeric peptide (page 158). Accordingly, Kaumaya et al. teaches the multivalent chimeric peptides are capable of bypassing haplotype restriction associated with a B cell epitope (page 158).

Lairmore et al. teaches also teaches a composition of *multivalent chimeric peptides*, which comprises a plurality of the same or different B cell epitopes and a plurality of T helper cell epitopes covalently attached to either strand of a "β sheet template", which is a polypeptide comprising two strands of alternating leucine and lysine residues connected by a linker of 6 amino acids; see entire document, particularly page 6078, Figure 1. The linker adjoining the two strands of alternating residues consists of the amino acid sequence, Gly-Leu-Pro-Ser-Gly-Gly (page 6078, Figure 1). As further depicted in Figure 1, Lairmore et al. teaches at least one of the different B cell epitopes and the T helper epitope, which are affixed to the "template", are adjoined by a linker of 1 to 15 amino acids. For example, Lairmore et al. teaches the T helper epitope "MVF" is connected to the B- and T-cell epitopes "SP2" and SP4a" by a linker of 12 and 14 amino acids, respectively (page 6078, Figure 1).

The obviousness of the claimed invention:

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a multivalent chimeric peptide comprising a HER-2 B cell epitope comprising SEQ ID NO: 42, a HER-2 B cell epitope comprising SEQ ID NO: 1, and a T helper cell epitope, which is any of the promiscuous T helper epitopes taught by Kaumaya et al. or the same or functional equivalent taught by Woodbine, adjoined to a polypeptide consisting of two strands of alternating leucine and lysine residues

connected by a linker, as described by Kaumaya et al. and Lairmore et al., because Woodbine teaches a HER-2 B cell epitope comprising SEQ ID NO: 42, whereas Fendly et al. teaches a HER-2 B cell epitope comprising SEQ ID NO: 1, both of which are effective immunogens to elicit an immune response that produces antibodies that bind to and inhibit the growth of cancer cells expressing HER-2, and because while Woodbine teaches that colinear chimeric peptides comprising the B cell and T cell epitopes adjoined by a linker elicit antibodies reactive against different epitopes of the extracellular domain of HER-2, which bind to tumor cells expressing HER-2 to retard their growth, Kaumaya et al. teaches that such a multivalent chimeric peptide is more immunogenic than the colinear chimeric peptides of Woodbine and are capable bypassing haplotype restriction associated with a B cell epitope, raising antibodies against the B cell epitope in animals of different haplotypes, which do not respond to such colinear peptides. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to produce a composition that can be used to bypass haplotype restriction to more effectively produce antibodies that retard the growth of HER-2-positive tumors.

Conclusion

18. Claim 35 is allowed; but no other claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent Application Publication Nos. 2003/0170235 A1 and 2004/0037823 A9 teach a peptide comprising the HER-2 B cell epitope having the amino acid sequence identified in the instant application as SEQ ID NO: 1.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
September 7, 2005